Estimation of Pharmacokinetic Model Parameters

Aleksandar Timcenko, Ph.D., David L. Reich, M.D., Giuseppe Trunfio, M.D.*

{timcenko|dreich}@smtplink.mssm.edu
Department of Anesthesiology
Mount Sinai Medical Center
One Gustave Levy Place
New York, NY 10029

* trunfio.giuseppe@new-york.va.gov
Veterans Administration Medical Center
423 E.23rd Street
New York, NY10010

Abstract

This paper addresses the problem of estimating the depth of anesthesia in clinical practice where many drugs are used in combination. The aim of the project is to use pharmacokinetically-derived data to predict episodes of light anesthesia. The weighted linear combination of anesthetic drug concentrations was computed using a stochastic pharmacokinetic model. The clinical definition of light anesthesia was based on the hemodynamic consequences of autonomic nervous system responses to surgical stimuli. A rule-based expert system was used to review anesthesia records to determine instances of light anesthesia using hemodynamic criteria. It was assumed that light anesthesia was a direct consequence of the weighted linear combination of drug concentrations in the patient's body that decreased below a certain threshold. We augmented traditional two-compartment models with a stochastic component of anesthetics' concentrations to compensate for interpatient pharmacokinetic and pharmacodynamic variability.

A cohort of 532 clinical anesthesia cases was examined and parameters of two compartment pharmacokinetic models for 6 intravenously administered anesthetic drugs (fentanyl, thiopenthal, morphine, propofol, midazolam, ketamine) were estimated, as well as the parameters for 2 inhalational anesthetics (N_2O and isoflurane). These parameters were then prospectively applied to 22 cases that were not used for parameter estimation, and the predictive ability of the pharmacokinetic model was determined. The goal of the study is the development of a pharmacokinetic model that will be useful in predicting light anesthesia in the clinically relevant circumstance where many drugs are used concurrently.

1 Introduction

The aim of general anesthesia is to provide unconsciousness, analgesia, amnesia and muscle relaxation for patients undergoing surgical procedures. The degree (or "depth") of anesthesia should be adequate for the surgical stimulus. Too deep a plane of anesthesia may produce negative consequences, such as hypotension and/or delayed emergence from anesthesia, while an inappropriately light level of anesthesia may result in the recall of intraoperative events or potentially unfavorable hemodynamic events, such as hypertension and tachycardia (which represent autonomic nervous system responses to surgical stimuli). No reliable monitor of depth of anesthesia exists at present[1]. Thus, the anesthesiologist continually titrates the quantities of anesthetic drugs administered to the patient according to experience and hemodynamic responses. Typically, the anesthesiologist will have to administer additional drug(s) at various points during an anesthetic when noxious stimuli in hemodynamic changes indicating light anesthesia.

Mathematical pharmacokinetic models have been developed in order to facilitate the maintenance of an appropriate anesthetic level[2]. These models are designed to achieve a target plasma concentration reputed to be optimal for anesthetic effect. Unfortunately, these models are commonly based on mono-drug therapy, which is rare in clinical practice[3]. Another problem with this approach is marked interindividual pharmacokinetic/pharmacodynamic variability

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that complicates the maintenance of the desired plasma concentration[4].

This paper addresses the problem of estimating parameters of pharmacokinetic models during clinical anesthetics involving multiple drugs. The estimation process optimizes the criterion that is based on the output of the anesthesiology expert system[5]. The expert system uses a set of rules that determine the state of light anesthesia from hemodynamic measurements, such as heart rate and blood pressure. The case files were generated using the CompuRecord® data acquisition system [Anesthesia Recording, Inc., Pittsburgh, PA].

For this analysis, we divided anesthetic drugs into two categories: intravenous and inhalational. For each intravenous drug, we derived a two-compartment model* , and for each inhalational drug we determined a weighted constant (of the alveolar concentration) that indicated how much the anesthetic contributed to the overall depth of anesthesia. We assumed that all anesthetics contributed linearly (with different weight factors) to the overall depth of anesthesia, and that below a certain level (Z_0), the depth of anesthesia was considered to be "light." This level was arbitrarily selected to be $Z_0 = 1$.

The traditional two-compartment model[6] was augmented with a stochastic component that allowed for interindividual variability in determining the drug concentration and effect. Thus, the augmented model generates a probability distribution of multiple drugs' effects.

2 Methods

2.1 Pharmacokinetic Modeling

We have devised an augmentation of the standard two-compartment model that includes the random disturbance superimposed on drug concentrations in central and peripheral compartments (Figure 1.). The mathematical model of the drug elimination can be expressed in the canonical form as

$$\begin{aligned} d\mathbf{x} &= A\mathbf{x}dt + Budt + \Sigma d\mathbf{W} \\ y &= C\mathbf{x} \end{aligned} \qquad (1)$$

where $\mathbf{x} = [\, x_1 \;\; x_2 \,]^T$ is the vector of drug concentrations in the central and peripheral compartment respectively and A, B, Σ and C are matrices given by:

$$A = \begin{bmatrix} -k_{10} - k_{12} & k_{21} \\ k_{12} & -k_{20} - k_{21} \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix},$$

$$B = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \; \Sigma = \begin{bmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{bmatrix} \text{ and } C = \begin{bmatrix} c_1 & 0 \end{bmatrix}.$$

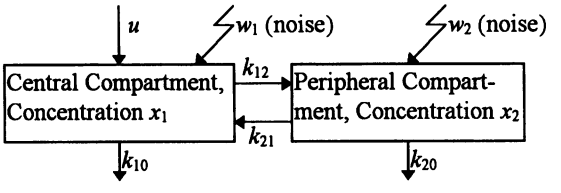

Figure 1. Stochastic two-compartment model

Stochastic systems theory states that[7] the output of a system described by the model (1) is a normally distributed random variable with the mean m and variance σ^2 (defined as outputs of two linear deterministic dynamical systems). These two systems are defined by an 8-tuple of parameters $\mathbf{q} = (a_{11}, a_{12}, a_{21}, a_{22}, c_1, \gamma_{11}, \gamma_{12}, \gamma_{22})$ where the matrix $\Gamma = \Sigma\Sigma^T = \begin{bmatrix} \gamma_{11} & \gamma_{12} \\ \gamma_{12} & \gamma_{22} \end{bmatrix}$ appears in the model for the variance σ^2.

The dynamic behavior of a stochastic pharmacokinetic model is illustrated in Figure 2. (The standard deviations in Figure 2 are exaggerated to demonstrate their exponential increase. In reality, gaussian distributions describing the concentrations' distribution are much narrower.). The physically acceptable range of drugs' concentrations is anywhere between the initially administered concentration and 0. In Figure 2, physically unacceptable values for drugs' concentrations are displayed in gray. From the linearity of the stochastic model, we derive the drug concentration Z as a random variable with the gaussian distribution. The mean of the concentration exponentially decay towards 0, and the standard deviation exponentially increases.

* The two-compartment model was used due to the computational complexity of estimating three-compartment model. Since the three-compartment model is more standard[10], we will address the problem of parameter estimation of the three compartment model in the future work.

Since the random variable Z is normally distributed with mean $m = \Sigma c_i m_{i1}$ and standard deviation $\sigma^2 = \Sigma c_i^2 \sigma_i^2$, we can compute the probability $P\{Z < Z_0 \mid Z \leq Z(0), Z \geq 0\}$ in the closed form using the error function (for brevity this calculation is omitted in this paper). This probability is interpreted as the likelihood of light anesthesia.

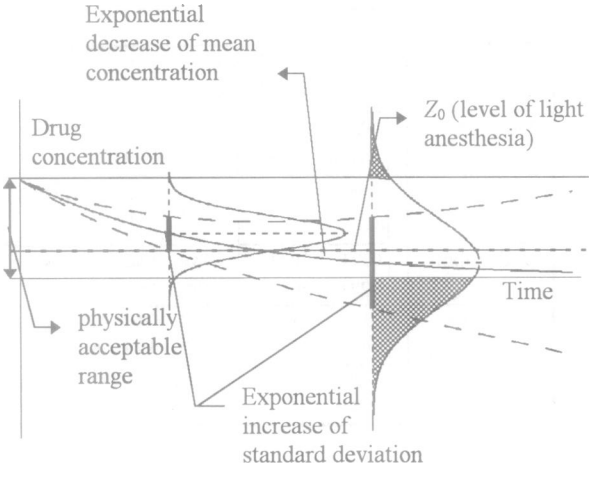

Figure 2. The mean drug concentration (solid line), the standard deviation (dashed lines) and the level of light anesthesia

2.2 Expert System Assessment of Light Anesthesia

In order to determine the state of light anesthesia, we applied a rule-based expert system[1] to a cohort of cases. The state *light anesthesia* was defined using physiologic measurements and their trends. The program for examining case files was designed using the temporal query language QL that creates highly efficient C code. The rules for light anesthesia are shown in Figure 3.

```
light_anesthesia =
   trend condition MAP within 5 min increasing and
   trend condition CVP within 5 min increasing and
   OR
   trend condition HR within 5 min increasing
   OR
   condition MAP high and
   trend condition MAP within 5 min labile
   OR
   condition HR high and
   trend condition HR within 5 min labile
```

Figure 3. Rule for *light anesthesia.*
(Abbreviations: MAP = mean arterial pressure, CVP = central venous pressure, HR = heart rate)

We assumed that the state of light anesthesia, as determined by the expert system, had to coincide with light anesthesia predictions based on the pharmacokinetic model. Using this premise, we developed the estimation scheme shown in Figure 4.

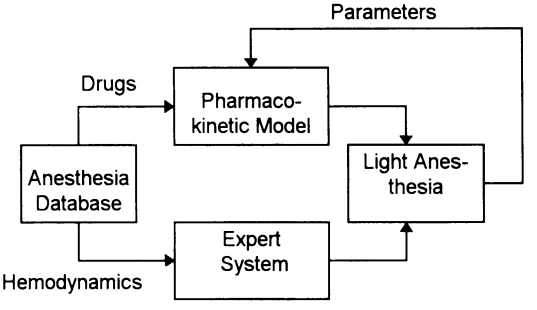

Figure 4. Estimation of pharmacokinetic model parameters

The expert system determines the state of light anesthesia as a binary event,

$E(\text{light\_anesthesia}) \in \{0, 1\}$.

The pharmacokinetic model estimates the depth of anesthesia (Z) as a weighted linear combination of drugs' concentrations in the central compartment:

$$Z = \Sigma c_i x_{i1} \qquad (2)$$

where c_i is the (unknown) weight factor for drug i, x_{i1} is the central compartment concentration for drug i, and the summation is done over all drugs. Each drug's concentration is considered to be a normally distributed random variable whose mean m_i and standard deviation σ_i are given by the pharmacokinetic model. The probability that the patient has light anesthesia at the present is considered to be the probability that the estimated depth of anesthesia is below certain prescribed level Z_0. We require that the drug's concentration is within physically acceptable boundaries (below the initially administered concentration and above 0):

$P(\text{light\_anesthesia}) = P\{Z < Z_0 \mid Z \leq Z(0), Z \geq 0\}$

where $Z(0)$ is the linear weighted sum of the initial concentration of all drugs that were administered.

2.3 Optimization Criterion

The objective of the estimation process is to determine the parameters of the pharmacokinetic model such that the probability of light anesthesia is numerically as close as possible to the binary event E(light_anesthesia) determined (from hemodynamic criteria) by the expert system. In particular, we define the optimization criterion:

$$J = \sum_{\text{all cases}} \int_{\substack{\text{case} \\ \text{begin}}}^{\substack{\text{case} \\ \text{end}}} (E - P)^2 \, dt \qquad (3)$$

where $E = E$(light_anesthesia) is the binary event determined by the expert system, $P = P$(light_anesthesia) is the probability that the concentration of drugs is below the critical level Z_0. The summation is done over all cases and, in each case, the squared difference between the observed light anesthesia (E) and the estimated light anesthesia (P) is integrated over the entire duration of the case. The optimization criterion J is a function of unknown parameters $\mathbf{q}$ of the pharmacokinetic models, $J = J(\mathbf{q})$. The objective of the optimization process is to find the vector of parameters $\mathbf{q}_{\min}$ that minimizes the criterion J: $J_{\min} = J(\mathbf{q}_{\min})$.

Once the optimization criterion J (3) is formulated, the parameters $\mathbf{q}$ are obtained through the numerical minimization of J. We have applied the simplex method [9] mainly due to its numerical robustness and ability to perform multivariate optimization without computing partial derivatives.

3 Results: Predictive Value of the Model

We have applied the estimation process on a cohort of 532 relatively homogeneous cases (limited to age range 13-40 years, ASA physical status classification 1-2, and general anesthesia). There were 8 different anesthetic drugs used in these cases: N_2O, isoflurane, propofol, fentanyl, midazolam, penthotal, morphine and ketamine. The results of the estimation process are shown in Tables 1 and 2.

Table 3 shows the comparison between redistribution and elimination half-lives for some of the intravenous drugs considered in this study with standard textbook figures[9]. The half-life times are computed as reciprocial values of eigenvalues of matrices A.

Drug	**Parameters**		
	A	Γ	c
Fentanyl	$\begin{bmatrix} -0.098 & 0.010 \\ -0.234 & 0.214 \end{bmatrix}$	$\begin{bmatrix} 0.008 & -0.002 \\ -0.002 & 0.007 \end{bmatrix}$	**0.004**
Morphine	$\begin{bmatrix} -0.169 & 0.011 \\ -0.018 & 0.002 \end{bmatrix}$	$\begin{bmatrix} 0.009 & 0.025 \\ 0.025 & 0.004 \end{bmatrix}$	**0.55**
Propofol	$\begin{bmatrix} 0227 & -0.048 \\ 0.205 & -0.026 \end{bmatrix}$	$\begin{bmatrix} 0.001 & 0.020 \\ 0.005 & 0.007 \end{bmatrix}$	**0.003**
Midazolam	$\begin{bmatrix} 0.124 & -0.029 \\ 0.229 & -0.049 \end{bmatrix}$	$\begin{bmatrix} 0.008 & -0.002 \\ -0.003 & 0.006 \end{bmatrix}$	**0.08**
Ketamine	$\begin{bmatrix} 0.115 & -0.003 \\ 0.948 & -0.018 \end{bmatrix}$	$\begin{bmatrix} -0.012 & 0.057 \\ 0.008 & -0.018 \end{bmatrix}$	**0.32**
Thiopental	$\begin{bmatrix} -0.153 & 0.028 \\ -0.248 & 0.026 \end{bmatrix}$	$\begin{bmatrix} -0.012 & -0.02 \\ -0.02 & 0.003 \end{bmatrix}$	**0.003**

Table 1. Estimated parameters for intravenous drugs

Drug	**Parameters**	
	c	σ^2
N_2O	0.34	0.040
Isoflurane	0.61	0.008

Table 2. Estimated parameters for inhalational drugs

Drug	Half life		Half life (from [10])	
	$t_{1/2\alpha}$	$t_{1/2\beta}$	$t_{1/2\alpha}$	$t_{1/2\beta}$
Fentanyl	14	145	20	180
Thiopental	10	33	6.8	60
Morphine	6	242	15	180

Table 3. Comparison of half-lives between the parameters obtained in this paper and elsewhere

The derived pharmacokinetic models were applied prospectively to a set of 22 cases that were not used in the parameter estimation process. The expert system reported 104 instances of light anesthesia and the pharmacokinetic model predicted 68 instances. One possible source of

error is that the pharmacokinetic parameters were estimated using data from 30 minutes after the start of the case until 30 minutes prior to the end of the case. Thus, the "gain" parameters may be set too low to handle the noxious stimulation of tracheal intubation at the beginning of the case and emergence from anesthesia at the end of the case.

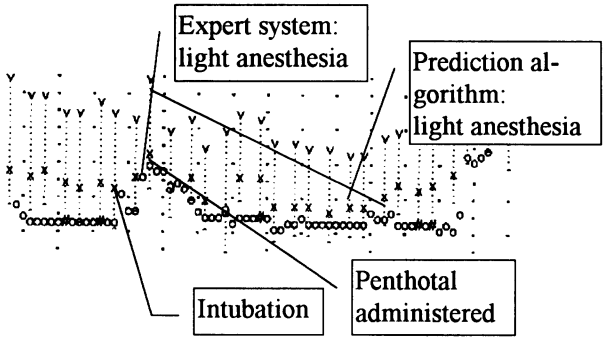

Figure 5. Case example: instances of light anesthesia reported by the expert system and by the prediction algorithm

4 Conclusion

This paper addresses the problem of predicting episodes of light anesthesia using a pharmacokinetic model for multiple drug anesthetics. The method that we applied was a comparison of light anesthesia (based on an expert system's interpretation of patient hemodynamics) with the estimated depth of anesthesia as computed in the pharmacokinetic model. As a significant departure from traditional two-compartment pharmacokinetic models, we have devised a *stochastic* model that computes the distribution of drug concentrations. The advantage of this formulation is that it offers a *probability* of light anesthesia in addition to the estimated depth of anesthesia. Initial results have yielded pharmacokinetic parameters that are similar to previously published results. Nevertheless, further work will be required to confirm the clinical usefulness of this method in a prospective fashion.

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A The Stochastic Model

The solution of the stochastic differential equation (1) is a random variable whose probability distribution density function $\psi(t, \boldsymbol{x})$ is given as a solution of the Fokker-Planck partial differential equation (also known as forward Kolmogorov equation). It is known in the theory of stochastic differential equations[7] that, for constant A, B and Σ, the solution of equation (1) is the gaussian distribution with density function

$$\psi_{\mathbf{x}} = \frac{1}{2\pi|V|} e^{-\frac{1}{2}(\mathbf{m}-\mathbf{x})^T V^{-1}(\mathbf{m}-\mathbf{x})}$$

where the expectation $\mathbf{m}$ and the covariance matrix V are defined through the model parameters.